REMARKS

The Applicant has herein amended Claims 1, 11, and 21. Claim 1 is now directed to a computer-aided method of identifying a ligand that binds to a protein and includes the steps of calculating a score based on the optimized position of the ligand that is predictive of the ligand's potential to bind to the protein and identifying the ligand as a ligand that binds to the protein if the score is above a threshold. Claim 11 is now directed to a computer-aided system for identifying a ligand that binds to a protein and includes means for calculating a score based on the optimized position of the ligand that is predictive of the ligand's potential to bind to the protein and means for identifying the ligand as a ligand that binds to the protein if the score is above a threshold. Claim 21 is now directed to program storage device readable by a machine, tangibly embodying at least one program of instructions executable by the machine to perform a method of identifying a ligand that binds to a protein, where the method includes the steps of calculating a score based on the optimized position of the ligand that is predictive of the ligand's potential to bind to the protein and identifying the ligand as a ligand that binds to the protein if the score is above a threshold.

Support for identifying ligands that bind to a protein may be found, for example, in the specification at page 1, lines 1-2 ("identification of binding ligands"); page 20, last paragraph ("This approach...attempts to match interactions between the ligand and receptor."); and the general discussion throughout the specification and documents cited in the specification that refer to docking of ligands to proteins and binding of ligands to proteins. Support for calculating a score predictive of the ligand's potential to bind to the protein may be found, for example, in the specification at page 17, last paragraph, to page 20, first full paragraph (describing the calculation of a simple atom pairwise score); pages 22-24, table 1 (presenting rms deviations between crystallographically observed ligand binding positions and the top scoring predicted ligand binding positions); page 27, second paragraph (indicating that for test runs, "the top scoring docked position and the observed position" had "little difference," demonstrating that the top scoring docked positions were indicative of actual ligand binding); and page 29 to page 30, first paragraph (presenting three actual examples demonstrating that the best scoring docked position was indicative of actual ligand-protein binding position). Support for identifying a ligand as a ligand that binds to the protein if the score is above a threshold may be found, for example, in

the specification at page 28, first paragraph (indicating that for the test runs, "well docked positions, i.e., low rms deviations" from actual ligand binding positions are indicated by a "10% cutoff" in score).

Claims 1-30 remain pending in the application. The Applicant has carefully considered all of the Examiner's rejections but respectfully submit that the pending claims are allowable for at least the reasons presented below.

Rejections under § 112 – Written Description and Enablement

The Examiner rejected Claims 1-30 under 35 U.S.C. § 112, ¶ 1 for failing to comply with the written description and enablement requirements. The Examiner asserted that the phrase "so as to identify ligands likely to have a therapeutic activity" constituted new matter. The Examiner also asserted that the claimed program/steps are not in themselves sufficient to identify ligands likely to have therapeutic activity. The Applicants have amended the claims to remove this phrase, thereby obviating the rejection. The Applicants note that as presently amended, the claims are directed to identifying ligands that bind to proteins and that such identification finds support in the specification, for example, as cited above.

Although the claims have been amended, the applicant would like to make some comments about the Examiner's position on this point. In the Office Action, the Examiner asserts that "the mere fact that a compound 'fits' or may dock into a binding site of a protein does not imply anything about the activity of a compound" and that "[m]ere knowledge that a compound binds to a site does not necessarily identify the compound as having therapeutic activity." The applicant wishes to point out that even though knowledge that a compound binds to a binding site is not alone sufficient to demonstrate therapeutic activity for the compound, knowledge that a compound binds to a protein of therapeutic interest does demonstrate that the compound is more likely to have therapeutic activity than compounds that do not bind to that protein. Most searches for new pharmaceuticals start with a screening of compounds from a compound library to identify "hits" that bind to the target of interest. These hits are explored further, while the remaining compounds are not because the scientists recognize that "hits" are more likely to be effective drugs than non-hits. In the past, such screening was done with *in-vitro* chemical testing. More recently, software modeling techniques have been developed to

perform screening *in-silico*, further improving hit identification speed and accuracy. Pharmaceutical companies spend large amounts of time and money to identify hits, and the reason is that hits are more likely to be good drugs than non-hits.

Thus, the patent application does describe a method by which a library of compounds can be screened to identify a subset of compounds that are likely to have therapeutic activity, where the term "likely" is intended to mean more likely than the compounds in the library that have low binding capacity.

Rejections under § 101 – Utility

The Examiner rejected Claims 1-30 under 35 U.S.C. § 101 for lack of patentable utility. The Examiner argued that because the claims do not recite any steps and the specification does not provide support for identifying a ligand likely to have therapeutic activity, the specification and claims do not support a utility. The Applicants have amended Claims 1-30 so that they are directed to identifying a ligand that binds to a protein. As discussed above, identifying a ligand that binds to a protein is useful. This utility is described in the specification by its statements regarding efficiency and cost effectiveness in prioritizing compounds for further study and its specific examples of proteins where it is desirable to find ligands that bind to the proteins. The Applicants respectfully submit that those of skill in the art reading the present specification would recognize many circumstances where it would be beneficial to identify ligands that bind to proteins.

In one application, the claimed invention reduces the time required to develop a pharmaceutical product because rather than testing all compounds in a set of compounds for potential activity at a protein, only those compounds that are predicted by the claimed invention to bind to the protein need be tested. The Examiner pointed out that both activators and inhibitors may bind to the same site of a protein or enzyme. However, regardless of whether the researcher is searching for an activator or an inhibitor, the claimed invention will significantly reduce research time in finding that activator or inhibitor because compounds that do not bind to the protein (and thus that cannot be either an activator or inhibitor) are not needlessly synthesized and/or tested. Accordingly, the claimed invention provides methods and systems that will save lives by getting needed drugs to patients sooner than would otherwise be possible.

Rejections under § 101 – Non-statutory Subject Matter

The Examiner rejected Claims 1-20 as being directed to non-statutory subject matter. With respect to Claims 1-10, the Examiner asserted that the claims did not recite a concrete, tangible, and useful result because no identification step was recited for identifying a ligand likely to have therapeutic activity. The Examiner stated that simply fitting a ligand into a protein does not indicate anything about possible therapeutic activity. The Applicant has herein amended Claims 1-10 so that they are directed to a process of identifying a ligand that binds to a protein. The claims now include the step of identifying a ligand as a ligand that binds to a protein if a score is above a threshold. As such, practicing the process of Claims 1-10 will produce the result of indicating whether a ligand will bind to a protein. This result is concrete, tangible, and useful.

The result is concrete and tangible because it provides a clear indicator to the user of whether or not the ligand will bind. The result is useful because, as indicated in the specification and as described above, it provides "prioritization tools [that] allow scientists to both obtain leads in a cost effective and efficient manner and to test virtual libraries against novel targets prior to active synthesis and bioanalysis, thereby, reducing synthesis costs." Specification, page 1, paragraph 2. Thus, when a target protein is identified for which it is desirable to have a ligand that binds to the protein, scientists can use the claimed invention to determine whether a candidate ligand will bind to the protein before investing the time, costs, and resources of synthesis and/or experimental analysis of the ligand. Such a benefit is of tremendous utility to those seeking to find and develop compounds that bind to specific proteins.

Those of skill in the art would recognize many proteins for which it is desirable to have a ligand bind to the protein. For example, the instant specification discusses compounds targeted to gp41 in HIV type 1 virus (page 2, second paragraph), molecular docking to thrombin, thermolysin, and neuramindidase (page 10, first paragraph), inhibitor binding to trypsin and trypsinogen (page 29, first paragraph), inhibitor binding to HIV proteases (page 29, second and third paragraphs), inhibitor binding to glutathione s-transferase (page 31, second paragraph), inhibitor binding to influenze virus neuraminidase (page 32, first paragraph), and inhibitor

binding to 1hef HIV type 1 protease (page 32, second paragraph). Thus, a technique, such as provided by the claimed invention, for identifying ligands that bind to these proteins is useful.

Furthermore, the instant specification references 103 proteins listed in the Protein Data Bank (PDB). Those of skill in the art would recognize many proteins in the PDB for which finding ligands that bind to the proteins would have pharmaceutical applications. For example, the 1999-2000 Protein Data Bank Annual Report, which is attached as Exhibit A, states that "[t]he 3-D structures of proteins and other biological macromolecules contained in the PDB hold significant promise for the pharmaceutical and biotechnology industries in the search for new drugs with few or no side effects." Accordingly, Claims 1-10 recite a process that produces a concrete, tangible, and useful result and are therefore directed to statutory subject matter.

With respect to Claims 11-20, the Examiner argued that the claims do not recite any structural or physical limitations and are thus merely a series of instructions to a computer and are non-statutory subject matter. The Applicants respectfully point out that Claims 11-20 contain means-plus-function clauses and thus must be interpreted by the Examiner in accordance with 35 U.S.C. § 112, ¶ 6. Accordingly, the claims must be "construed to cover the corresponding structure [or] material...described in the specification and equivalents thereof." 35 U.S.C. § 112, ¶ 6, see also M.P.E.P § 2181. Because each means clause must be construed to cover a structure or material disclosed in the specification, the Applicants respectfully submit that Claims 11-20 are clearly product claims and are directed to statutory subject matter.

CONCLUSION

The Applicants respectfully submit that they have overcome all of the Examiner's rejections by the amendments and remarks herein. Accordingly, the Applicants respectfully submit that the pending claims are allowable and request timely issuance of a Notice of Allowance.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 9/2/04

By: _____

Thomas R. Arno
Registration No. 40,490
Attorney of Record
Customer No. 20,995
(619) 235-8550

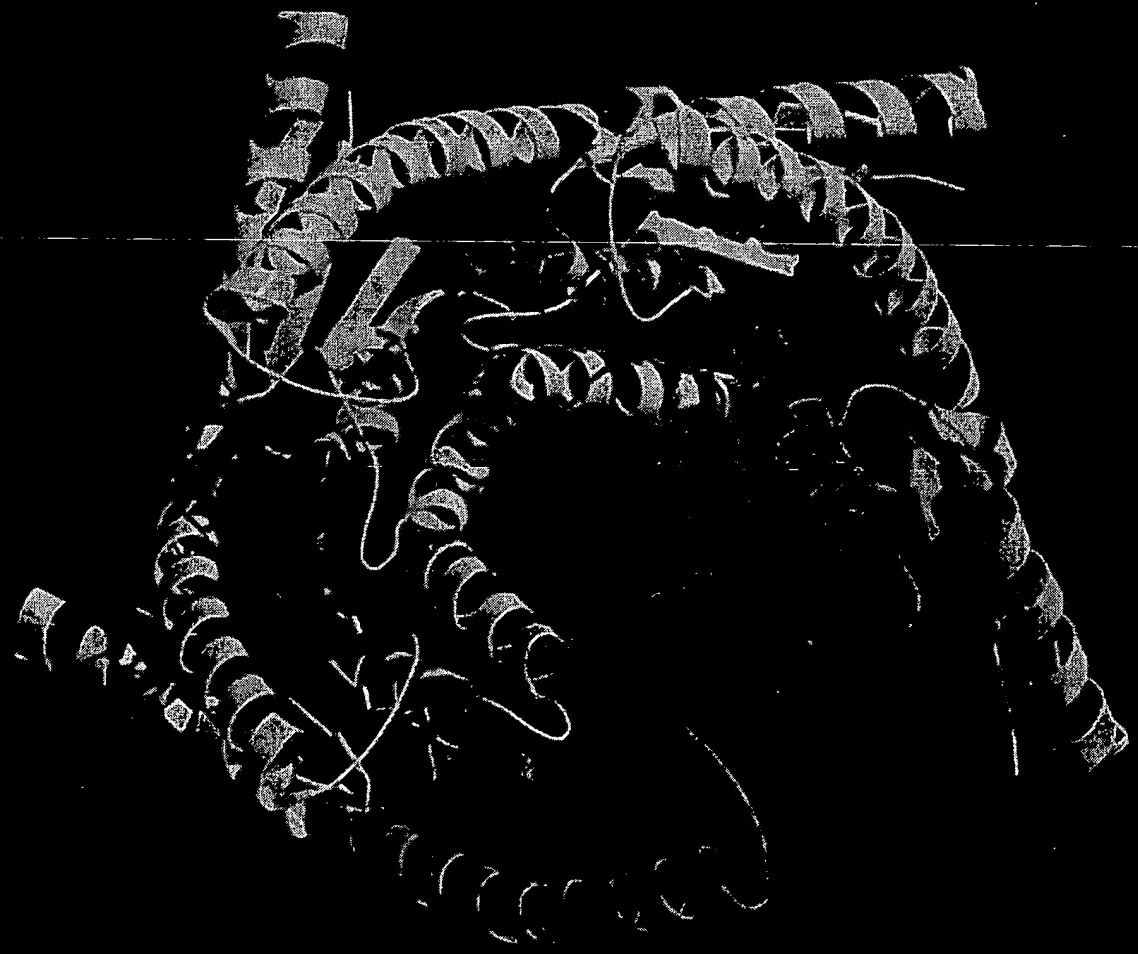
S:\DOCS\REM\REM-1622.DOC
083104

PROTEIN DATA BANK

PDB

ANNUAL REPORT

JULY 1999-JUNE 2000



RESEARCH COLLABORATORY FOR STRUCTURAL BIOINFORMATICS

• RUTGERS, THE STATE UNIVERSITY OF NEW JERSEY • NATIONAL INSTITUTE OF STANDARDS AND TECHNOLOGY •
• SAN DIEGO SUPERCOMPUTER CENTER AT THE UNIVERSITY OF CALIFORNIA, SAN DIEGO •

What is the PDB?

The Protein Data Bank is the sole international repository for 3-dimensional structure data of biological macromolecules. Specifically, it is a resource that processes, stores, and disseminates structure coordinates and related information about proteins, nucleic acids, nucleic acid complexes, viruses, polypeptides, and some carbohydrates.

Why is it important?

The 3-D structures of proteins and other biological macromolecules contained in the PDB hold significant promise for the pharmaceutical and biotechnology industries in the search for new drugs with few or no side effects, and the efforts to understand the mystery of human disease. Medical researchers envision gaining new insights into the causes, effects, and treatment of various diseases by unlocking the therapeutic potential of biological macromolecules. This requires very precise and accurate information about the atomic structure of complex molecules. The understanding of what a structure looks like aids in understanding how it works.

The PDB provides researchers with a rich source of information about biological structures. Because of the improvements that the RCSB has introduced, PDB users can now access new services and formulate complex queries that will provide reliable answers to further the research efforts of the international biological and biomedical communities. The PDB now provides powerful tools to help researchers understand biological function through investigation of sequence and molecular structure. The tremendous influx of data that is being fueled by the structural genomics initiative, and the increased recognition of the value of structural data in understanding biological function, demand new ways to collect, organize, and distribute data. The PDB will continue to meet this demand using the most modern technology that facilitates the use and analysis of structural data and that creates an enabling resource for biological research.

Who is involved in running it?

The PDB is managed by the Research Collaboratory for Structural Bioinformatics. The RCSB is a non-profit consortium composed of Rutgers, the State University of New Jersey; the National Institute of Standards and Technology (NIST); and the San Diego Supercomputer Center (SDSC), an organized research unit of the University of California at San Diego (UCSD). The RCSB is supported by funds from the National Science Foundation, the Department of Energy, and two units of the National Institutes of Health: the National Institute of General Medical Sciences and the National Library of Medicine.

The RCSB Project Team manages the overall operation of the PDB. Director Helen M. Berman, Professor of Chemistry at Rutgers, was part of the original team that developed the PDB in 1971 and is the founder of the Nucleic Acid Database. Data deposition and processing are the responsibilities of the RCSB Team at Rutgers, which is led by John Westbrook, Research Associate Professor of Chemistry. Data uniformity, NMR, and the master archive are the responsibilities of the RCSB Team at NIST, which is led by Gary Gilliland, Chief of the Biotechnology Division of the Chemical Science and Technology Laboratory. Data query and distribution functions are the responsibility of the RCSB Team at SDSC, which is led by Phil Bourne, Professor of Pharmacology at UCSD and Senior Principal Scientist at SDSC, and Peter Arzberger, Executive Director of SDSC.

Mission

The mission of the RCSB is to enable science worldwide by providing resources to improve our understanding of structure-function relationships in biological systems. The RCSB integrates a variety of production-level data and software resources, and shares research results and software. The RCSB is dedicated to fostering new scientific advances by providing accurate, consistent, well-annotated 3-D structure data that is delivered in a timely and efficient way to a wide audience. The RCSB will continue to significantly extend the capabilities of the PDB.

Historical background

The PDB was established at the Brookhaven National Laboratory (BNL) in 1971, initially holding 7 structures (Bernstein et al. 1977). After 27 years, responsibility for the operation and enhancement of the Protein Data Bank transitioned from BNL to the RCSB during the period from October 1998 to June 1999. Since July 1, 1999, the RCSB has had sole responsibility for the management of the PDB (Berman et al. 2000).

PDB Holdings (27-Jun-2000)

Experimental Technique	Molecule Type				
	Proteins, Peptides, and Viruses	Protein/Nucleic Acid Complexes	Nucleic Acids	Carbohydrates	Total
X-ray Diffraction and Other	9320	467	515	14	
NMR	1605	65	321	4	
Theoretical Modeling	246	18	17	0	
Total	11171	550	853	18	